

REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested and such action is earnestly solicited.

As correctly stated in the Official Action, Claims 21-25, 27-34, and 45-63 are pending in the present application. Claims 21-25, 27-34, and 45-63 stand rejected.

By the present amendment, Claims 31 and 58 have been amended to be consistent with the independent claims from which they depend. Claim 53 has been amended to correct a typographical error and to be consistent with Claim 58. No new matter has been added.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 31 and 58 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting "a compound consisting of an admixture of ... compounds." Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, Claims 31 and 58 have been amended to be consistent with the independent claims from which they depend. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 21-22, 24-25, 29-31, 45, 48-49, 51-58 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pruche et al. (FR 2787319). This rejection is respectfully traversed.

The Examiner notes that Pruche et al. disclose "a method of applying a composition comprising 4,5-dihydroxystilbene-3-O-beta-D glucoside, a physiologically acceptable medium and additives to keratinous materials such as hair." However, that the disclosed composition in Pruche et al. are used for dyeing the hair. Dyeing compositions were applied to the keratinous materials, not to the skin or the hair follicles.

To the contrary, the presently claimed invention comprises topically applying on the skin or the hair follicles, for a period of time sufficient, the compositions consisting of (i) glycosylated hydroxystilbene, (ii) one or more usual cosmetic or pharmaceutical additives and (iii) a physiologically acceptable medium. Applicants presume that the Examiner's rejection is based on the assumption that the result disclosed in the present invention would be inherently obtained when carrying out the method disclosed by Pruche et al. However, "to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999).

In the present case, in view of the fact that the compositions are used for dyeing, it is not predictable whether the compositions, being essentially applied to the keratinous materials and not to the skin or the hair follicles, would be applied in an effective amount and for a sufficient period of time for obtaining the claimed results of the presently claimed method, *e.g.*, for combating signs of aging of the hair follicles.

Applicants respectfully submit that Pruche et al. do not disclose or suggest each and every element of the claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 21-25, 27-34, 45, and 48-60 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Pezzuto et al. (WO 01/30336). This rejection is respectfully traversed.

The Examiner notes that "Pezzuto et al. teach a method for treating or preventing skin conditions such as those associated with sun damages and natural aging comprising topically administering a composition comprising a topical carrier and prodrug of resveratrol such as cis or trans resveratrol glucosides." The Examiner also indicates that "Pezzuto et al. teach reservatrol and its glucosides are art equivalents."

Applicants respectfully submit that Pezzuto et al. disclose the use of resveratrol glucoside among a variety of other derivatives of resveratrol:

Generally, the active agent will be cis-resveratrol, trans-resveratrol, or a complex in which one or more of the compounds hydroxyl groups are conjugated to a mono- or di-saccharide, *e.g.*, cis-resveratrol glucoside, trans-resveratrol glucoside, etc.

Page 6, lines 23-25.

Pezzuto et al. report at page 11, that cis-resveratrol glucoside and trans-resveratrol glucoside are particularly preferred among the derivatives of cis- and trans-resveratrol which comprise one hydroxyl group conjugated to a mono- or di-saccharide. However, Pezzuto et al. do not indicate why these products are preferred.

As Applicants have previously argued; the anti-oxidant effect for glycosylated and unglycosylated hydroxystilbenes have been investigated by Teguo et al. (*J. Nat. Prod.* 61:655-657 (1998)). The Teguo et al. publication reports that the glucosylated hydroxystilbenes tested (one of which is piceid) have anti-oxidant activities far inferior to the non-glucosylated hydroxystilbenes tested (one of which is resveratrol). Indeed, the reduction was seven times in the case of (E)-piceid versus resveratrol. Thus, the teachings of the two cited publications conflict. In this situation, the capacity of each reference to suggest solutions to one of ordinary skill in the art must be weighted, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 U.S.P.Q.2d 1089 (Fed. Cir. 1991).

In Teguo et al., the advantages of the non glucosylated hydroxystilbene over the glucosylated hydroxystilbenes are clearly shown by the results. This is opposed to Pezzuto et al., who allege possible use of glucosylated hydroxystilbene without providing any evidence for such alleged preference. All the compositions reported by Pezzuto et al. are formulated with resveratrol. The method is not exemplified with compositions comprising glucosylated resveratrol. Accordingly, weighing the suggestive power of each references,

and appreciating the teachings of the prior art as a whole, it is clear that the skilled artisan would not consider glucosylated hydroxystilbene as an art equivalent of non-glucosylated hydroxystilbene. Rather, one skilled in the art would prefer non-glucosylated hydroxystilbene because he would not have a reasonable expectation of success with glucosylated hydroxystilbene.

Thus, Applicants respectfully submit that Pezzuto et al. do not disclose or suggest the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 21-25, 27-34, and 45-63 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carson et al. (WO 99/04747), Pezzuto et al., and Teguo (*J. Nat. Prod.* 61:655-657 (1998)). This rejection is respectfully traversed.

Applicants have previously discussed the deficiencies of the Carson et al. publication in detail in the Reply & Amendment filed on May 5, 2003. *See particularly* pages 10-16. For example, Carson et al. do not disclose or suggest the possibility of using glucosylated resveratrol or any other glycosylated hydroxystilbene in their method.

The Examiner relies on the assumption that Pezzuto et al. allegedly disclose that resveratrol and its glucosides are art equivalents. As discussed above, this cannot be asserted when considering the prior art as a whole: the Teguo et al. publication most certainly demonstrates that this is not the case.

Applicants respectfully submit that the presently claimed invention also possesses surprising and unexpected results which confirm its nonobviousness. That is, the presently claimed invention discloses unexpected results and advantages for the use of glycosylated hydroxystilbene. First, the present specification discloses that glucosylated hydroxystilbene is slowly hydrolyzed by glycosidases which are naturally secreted by the skin or the hair follicles, thereby releasing the active agent, *i.e.*, the non-glucosylated hydroxystilbene. This is evidenced by the fact that the release can be enhanced in a dose-dependent manner by glucosidase activators.

The present specification also provides evidence that the glucosylated hydroxystilbenes are more stable. This is demonstrated in Example 1. In the presence of tyrosinase, which is a polyphenol oxidase, resveratrol is slowly released, indicating a resistance of the glucosylated derivative against oxidation. This unexpected advantage was further confirmed by Regev-Shoshani et al. (*Biochem. J.*, 374:157-163 (2003), attached hereto as Exhibit A). *See* table 3 and p. 160, § Tyrosinase activity towards resveratrol and its derivatives.

Finally, glucosylated hydroxystilbenes exhibit better solubility in aqueous medium. The cited publications do not disclose or suggest any of the advantages of the glucosylated hydroxystilbenes as disclosed in the present specification (summarized, *e.g.*, on page 2, lines 14-25).

Accordingly, in view of the generic disclosure in the prior art regarding the use of grape extract for cosmetic use and in view of the conflicting teachings of the prior art

regarding glucosylated stilbenes, one skilled in the art would not have been motivated to select the claimed species of glucosylated hydroxystilbene, as the main active ingredient. Moreover, the presently claimed invention possesses surprising and unexpected results. Thus, the presently claimed invention cannot be obvious over the cited publications. Withdrawal of this rejection is respectfully requested.

Conclusions

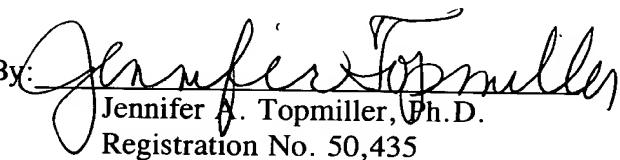
From the foregoing, further and favorable consideration of the subject application on the merits is respectfully requested and such action is earnestly solicited.

If there are any questions concerning this amendment, or the application in general, the Examiner is respectfully requested to telephone Applicant's undersigned representative so that prosecution may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: December 12, 2003

By: 
Jennifer A. Topmiller, Ph.D.
Registration No. 50,435

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620